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ADVANCED ORGANIC CHEMISTRY

REACTIONS, MECHANISMS, AND STRUCTURE

FOURTH EDITION

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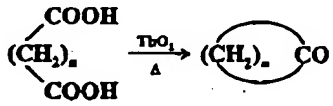
0-113 Ketonic Decarboxylation[1715]
Alkyl-de-hydroxylation

$$2RCOOH \xrightarrow[ThO_2]{400\text{-}500^\circ C} RCOR + CO_2$$

Carboxylic acids can be converted to symmetrical ketones by pyrolysis in the presence of thorium oxide. In a mixed reaction, formic acid and another acid heated over thorium oxide give aldehydes. Mixed alkyl aryl ketones have been prepared by heating mixtures of ferrous salts.[1717] When the R group is large, the methyl ester rather than the acid can be decarbmethoxylated over thorium oxide to give the symmetrical ketone.

The reaction has been performed on dicarboxylic acids, whereupon cyclic ketones are obtained:



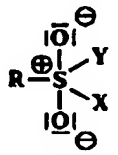
This process, called *Ruzicka cyclization*, is good for the preparation of rings of 6 and 7 members and, with lower yields, of C_8 and C_{10} to C_{30} cyclic ketones.[1718]

Not much work has been done on the mechanism of this reaction. However, a free-radical mechanism has been suggested on the basis of a thorough study of all the side products.[1719]

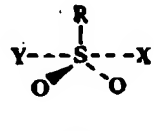
OS I, 192; II, 389; IV, 854; V, 589. Also see OS IV, 55, 560.

Nucleophilic Substitution at a Sulfonyl Sulfur Atom[1720]

Nucleophilic substitution at RSO_2X is similar to attack at RCOX. Many of the reactions are essentially the same, though sulfonyl halides are less reactive than halides f carboxylic acids.[1721] The mechanisms[1722] are not identical, because a "tetrahedral" intermediate in this case (147) would have five groups on the central atom. Though this is possible (since sulfur



147



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can accommodate up to 12 electrons in its valence shell) it seems more likely that these mechanisms more closely resemble the SN2 mechanism, with a trigonal bipyramidal transition state (148). There are two major experimental results leading to this conclusion.

[1715]For a review, see Kwart; King, in Patai, Ref. 197, pp. 362-370.
[1716]Granito; Schultz *J. Org. Chem.* 1963, *28*, 879.
[1717]See, for example, Ruzicka; Stoll; Schinz *Helv. Chim. Acta* 1926, *9*, 249, 1928, *11*, 1174; Ruzicka; Brugger; Seidel; Schinz *Helv. Chim. Acta* 1928, *11*, 496.
[1718]Hiles; Biemann *J. Am. Chem. Soc.* 1972, *94*, 5772. See also Bouchoule; Blanchard; Thomassin *Bull. Soc. Chim. Fr.* 1973, 1773.
[1719]For a review of mechanisms of nucleophilic substitutions at di-, tri-, and tetracoordinated sulfur atoms, see Ciuffarin; Fava *Prog. Phys. Org. Chem.* 1968, *6*, 81-109.
[1720]For a comparative reactivity study, see Hirata; Kiyan; Miller *Bull. Soc. Chim. Fr.* 1988, 694.
[1721]For a review of mechanisms of nucleophilic substitution at a sulfonyl sulfur, see Gordon; Maskill; Ruasse *Chem. Soc. Rev.* 1989, *18*, 123-151.

1. The stereospecificity of this reaction is more difficult to determine than that of nucleophilic substitution at a saturated carbon, where chiral compounds are relatively easy to prepare, but it may be recalled (p. 98) that optical activity is possible in a compound of the form RSO_2X if one oxygen is ^{16}O and the other ^{18}O. When a sulfonate ester possessing this type of chirality was converted to a sulfone with a Grignard reagent (**0-119**), inversion of configuration was found.[1723] This is not incompatible with an intermediate such as **147** but it is also in good accord with an SN2-like mechanism with backside attack.

2. More direct evidence against **147** (though still not conclusive) was found in an experiment involving acidic and basic hydrolysis of aryl arenesulfonates, where it has been shown by the use of ^{18}O that an intermediate like **147** is not reversibly formed, since ester recovered when the reaction was stopped before completion contained no ^{18}O when the hydrolysis was carried out in the presence of labeled water.[1724]

Other evidence favoring the SN2-like mechanism comes from kinetics and substituent effects.[1725] However, evidence for the mechanism involving **147** is that the rates did not change much with changes in the leaving group[1726] and the ρ values were large, indicating that a negative charge builds up in the transition state.[1727]

In certain cases in which the substrate carries an α hydrogen, there is strong evidence[1728] that at least some of the reaction takes place by an elimination–addition mechanism (E1cB, similar to the one shown on p. 382), going through a *sulfene* intermediate,[1729] e.g., the reaction between methanesulfonyl chloride and aniline.

$$CH_3{-}SO_2Cl \xrightarrow{base} CH_2{=}SO_2 \xrightarrow{PhNH_2} CH_3{-}SO_2{-}NHPh$$

A sulfene

In the special case of nucleophilic substitution at a sulfonic ester RSO_2OR', where R′ is alkyl, R′—O cleavage is much more likely than S—O cleavage because the OSO_2R group is such a good leaving group (p. 353).[1730] Many of these reactions have been considered previously (e.g., **0-4**, **0-14**, etc.), because they are nucleophilic substitutions at an alkyl carbon atom and not at a sulfur atom. However, when R′ is aryl, then the S—O bond is much more likely to cleave because of the very low tendency aryl substrates have for nucleophilic substitution.[1731]

[1723]Sabol; Andersen *J. Am. Chem. Soc.* **1969**, *91*, 3603. See also Jones; Cram *J. Am. Chem. Soc.* **1974**, *96*, 2183.

[1724]Christman; Oae *Chem. Ind. (London)* **1959**, 1251; Oae; Fukumoto; Kiritani *Bull. Chem. Soc. Jpn.* **1963**, *36*, 346; Kaiser; Zaborsky *J. Am. Chem. Soc.* **1968**, *90*, 4626.

[1725]See, for example, Robertson; Rossall *Can. J. Chem.* **1971**, *49*, 1441; Rogne *J. Chem. Soc. B* **1971**, 1855, *J. Chem. Soc., Perkin Trans 2*, **1972**, 489; Gnedin; Ivanov; Spryskov *J. Org. Chem. USSR* **1976**, *12*, 1894; Banjoko; Okwuiwe *J. Org. Chem.* **1980**, *45*, 4966; Ballistreri; Cantone; Maccarone; Tomaselli; Tripoloue *J. Chem. Soc., Perkin Trans. 2* **1981**, 438; Suttle; Williams *J. Chem. Soc., Perkin Trans. 2* **1983**, 1563; D'Rozario; Smyth; Williams *J. Am. Chem. Soc.* **1984**, *106*, 5027; Lee; Kang; Lee *J. Am. Chem. Soc.* **1987**, *109*, 7472; Arcoria; Ballistreri; Spina; Tomaselli; Maccarone *J. Chem. Soc., Perkin Trans. 2* **1988**, 1793; Gnedin; Ivanov; Shchukina *J. Org. Chem. USSR* **1988**, *24*, 731.

[1726]Ciuffarin; Senatore; Isola *J. Chem. Soc., Perkin Trans. 2* **1972**, 468.

[1727]Ciuffarin; Senatore *Tetrahedron Lett.* **1974**, 1635.

[1728]For a review, see Opitz *Angew. Chem. Int. Ed. Engl.* **1967**, *6*, 107-123 [*Angew. Chem.* 79, 161-177]. See also King; Lee *J. Am. Chem. Soc.* **1969**, *91*, 6524; Skrypnik; Bezrodnyi *Doklad. Chem.* **1982**, *266*, 341; Farng; Kice *J. Am. Chem. Soc.* **1981**, *103*, 1137; Thea; Guanti; Hopkins; Williams *J. Am. Chem. Soc.* **1982**, *104*, 1128, *J. Org. Chem.* **1985**, *50*, 5592; Bezrodnyi; Skrypnik *J. Org. Chem. USSR* **1984**, *20*, 1660, 2349; King; Skonieczny *Tetrahedron Lett.* **1987**, *28*, 5001; Pregel; Buncel *J. Chem. Soc., Perkin Trans. 2* **1991**, 307.

[1729]For reviews of sulfenes, see King *Acc. Chem. Res.* **1975**, *8*, 10-17; Nagai; Tokura *Int. J. Sulfur Chem., Part B* **1972**, 207-216; Truce; Liu *Mech. React. Sulfur Compd.* **1969**, *4*, 145-154; Opitz *Angew. Chem. Int. Ed. Engl.* **1967**, *6*, 107-123 [*Angew. Chem.* 79, 161-177]; Wallace *Q. Rev. Chem. Soc.* **1966**, *20*, 67-74.

[1730]A number of sulfonates in which R contains α branching, e.g., $Ph_2C(CF_3)SO_2OR'$, can be used to ensure that there will be no S—O cleavage: Netscher; Prinzbach *Synthesis* **1987**, 683.

[1731]See, for example, Oae; Fukumoto; Kiritani *Bull. Chem. Soc. Jpn.* **1963**, *36*, 346; Tagaki; Kurusu; Oae *Bull. Chem. Soc. Jpn.* **1969**, *42*, 2894.

The order of nucleophilicity toward a sulfonyl sulfur has been reported as $OH^- > RNH_2 > N_3^- > F^- > AcO^- > Cl^- > H_2O > I^-$.[1732] This order is similar to that at a carbonyl carbon (p. 351). Both of these substrates can be regarded as relatively hard acids, compared to a saturated carbon which is considerably softer and which has a different order of nucleophilicity (p. 350).

0-114 Attack by OH. Hydrolysis of Sulfonic Acid Derivatives
***S*-Hydroxy-de-chlorination,** etc.

$$RSO_2Cl \xrightarrow{H_2O} RSO_2OH$$

$$RSO_2OR' \xrightarrow[H^+]{H_2O} RSO_2OH$$

$$RSO_2NR'_2 \xrightarrow[H^+]{H_2O} RSO_2OH$$

Sulfonyl chlorides as well as esters and amides of sulfonic acids can be hydrolyzed to the corresponding acids. Sulfonyl chlorides can by hydrolyzed with water or with an alcohol in the absence of acid or base. Basic catalysis is also used, though of course the salt is the product obtained. Esters are readily hydrolyzed, many with water or dilute alkali. This is the same reaction as **0-4**, and usually involves R'—O cleavage, except when R' is aryl. However, in some cases retention of configuration has been shown at alkyl R', indicating S—O cleavage in these cases.[1733] Sulfonamides are generally not hydrolyzed by alkaline treatment, not even with hot concentrated alkali. Acids, however, do hydrolyze them, though less readily than they do sulfonyl halides or sulfonic esters. Of course, ammonia or the amine appears as the salt. However, sulfonamides can be hydrolyzed with base if the solvent is HMPA.[1734]

OS I, 14; II, 471; III, 262; IV, 34; V, 406; VI, 652, 727. Also see OS V, 673; VI, 1016.

0-115 Attack by OR. Formation of Sulfonic Esters
***S*-Alkoxy-de-chlorination,** etc.

$$RSO_2Cl + R'OH \xrightarrow{base} RSO_2OR'$$

$$RSO_2NR''_2 + R'OH \xrightarrow{base} RSO_2OR' + NHR''_2$$

Sulfonic esters are most frequently prepared by treatment of the corresponding halides with alcohols in the presence of a base. The method is much used for the conversion of alcohols to tosylates, brosylates, and similar sulfonic esters. Both R and R' may be alkyl or aryl. The base is often pyridine, which functions as a nucleophilic catalyst,[1735] as in the similar alcoholysis of carboxylic acyl halides (**0-20**). Primary alcohols react the most rapidly, and it is often possible to sulfonate selectively a primary OH group in a molecule that also contains secondary or tertiary OH groups. The reaction with sulfonamides has been much less frequently used and is limited to N,N-disubstituted sulfonamides; that is, R'' may not be hydrogen. However, within these limits it is a useful reaction. The nucleophile in this case is actually $R'O^-$. However, R'' may be hydrogen (as well as alkyl) if the nucleophile is a phenol, so that the product is RSO_2OAr. Acidic catalysts are used in this case.[1736] Sulfonic acids have been converted directly to sulfonates by treatment with triethyl or trimethyl

[1732]Kice; Kasperek; Patterson *J. Am. Chem. Soc.* **1969**, *91*, 5516; Rogne *J. Chem. Soc. B* **1970**, 1056; Ref. 330.
[1733]Chang *Tetrahedron Lett.* **1964**, 305.
[1734]Cuvigny; Larchevêque *J. Organomet. Chem.* **1974**, *64*, 315.
[1735]Rogne *J. Chem. Soc. B* **1971**, 1334. See also Litvinenko; Shatskaya; Savelova *Doklad. Chem.* **1982**, *265*, 199.
[1736]Klamann; Fabicake *Chem. Ber.* **1960**, *93*, 252.